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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/812,702	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/8/07, 10/11/07, 9/17/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49 and 58-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49 and 58-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, further electing coronary artery disease and the marker CRTAM in the reply filed on 1/25/07 is acknowledged. Claims 52-57 are pending and examined in this office action.

Claim Rejections - 35 USC § 112

2. Claims 63, 64, 65, 72, 73, 74, 81, 82, 83, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, and 101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

3. In claim 63, 64, 65, 72, 73, 74, 81, 82, and 83, the limitation that the blood samples "comprises leukocytes which a have not been fractionated into cell types" is new matter. Such a recitation includes, for example, testing a blood sample where the red blood cells and the white blood cells have been separated, and also includes, the testing of whole blood RNA. There is clearly basis for the latter, but not the former.

4. Applicant asserts in the remarks that this claim limitation finds clear support in the specification, including figure 5C which shows standardized fractions of leukocytes. However, these are not leukocytes that have not been fractionated into cell types, as they have clearly been fractionated into cell types. While RNA levels have been determined in each of the fractions, this is not basis for the negative limitation "have not been fractionated into cell types." There is no discussion or example in the specification of the testing of RNA in blood samples which

comprise leukocytes which have not been fractionated into cell types. Applicant has attempted to present a claim which excludes a particular process step from a method (that is, fractionating the leukocytes) and then provides basis for the exclusion of the step in a method where the opposite occurred. This is not sufficient basis for the claim limitation because there is nothing in the specification that suggests applicant contemplated the exclusion of a step of fractionating leukocytes into cell types. Therefore, claims 63, 64, 65, 72, 73, 74, 81, 82, and 83, as well as all claims which depend from these claims are rejected for having new matter.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 51-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "unfractionated samples of lysed blood" is unclear in light of the prosecution history in this application and in the parent applications from which this application claims priority. The specification does not define what is meant by an "unfractionated samples of lysed blood." On its face, such a limitation appears to mean that the lysed blood sample is not separated into constituent parts, however, interpretation of the claim in light of the specification, pending claims, and applicant's remarks filed with the amendment results in ambiguity with regard to the meaning of this claim limitation.

An example in the specification which discusses lysis prior to quantification includes a centrifugation step after which the "pellet" is further treated. This is a fractionation after lysis but before quantification.

One might interpret detecting in "unfractionated sample of lysed blood" as requiring that the detection occur relative to RNA that was extracted from the entire blood sample without any prior separation into parts, which could be accomplished by direct extraction of the whole blood without separating removing the plasma from the blood sample, for example.

Applicant set forth still a different definition for a similar claim limitation in the remarks filed introducing a similar phrase into the claims in the parent application 10/268730. In discussing basis in the specification for the limitation, applicant stated that the limitation refers to "a sample of whole blood which has not been fractionated into cell populations and includes a drop of blood (see remarks dated 4/25/05, at page 5)." This definition for unfractionated sample of whole blood set forth by applicant would, therefore, allow a fractionation of the cellular material prior to RNA extraction (as exemplified in the instant specification in Example 5).

And so it is unclear what the metes and bounds of the phrase "unfractionated sample of lysed blood" actually encompasses in light of the lack of definition of the phrase in the specification and the many, conflicting possible interpretations in light of the specification, pending claims, and remarks by applicant.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 55-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation "unfractionated samples of lysed blood" appears to be new matter. The amendment which added this limitation did not cite support for the limitation. The specification teaches at page 43 treating a sample with lysing buffer, centrifuging the sample, and then processing the pellet with RT-PCR. Thus, the sample was fractionated prior to quantifying. The examiner was not able to identify basis for this limitation in the specification.

9. Claims 49 and 58-101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

The invention is drawn to a method detecting coronary artery disease in a human test subject, methods for testing for coronary artery disease and methods for testing CRTAM expression. All of the claims feature a step of quantifying a level of RNA encoded by CRTAM gene in a blood sample from a single test subject and comparing the lelvel with a quantified levle of RNA encoded by said gene in blood samples from control subjects having coronary artery disease. Some claims additionally include a comparison with a quantified level of RNA encoded by said gene in blood samples from control subjects that are healthy control subjects and/or control subjects not having said coronary artery disease.

Some claims set forth that a determination of a statistically significant similarity between the test level and the level of control subjects having said coronary artery disease "is indicative of said coronary artery disease."

Some claims set additionally forth that a determination of a statistically difference between the test level and a quantified level of RNA from control subjects not having said coronary artery disease and significant similarity between the test level and the level of control subjects having said coronary artery disease "is indicative of said coronary artery disease."

Some claims set additionally forth that a determination of a statistically difference between the test level and a quantified level of RNA from control subjects not having said coronary artery disease and significant similarity between the test level and the level of control subjects having said coronary artery disease "is indicative of said coronary artery disease."

The nature of the invention requires the knowledge of a reliable association between comparing CRTAM expression and the indication that coronary artery disease is present in a human. Further, the practice of the invention requires an understanding of how the presence of coronary artery disease effects the level of CRTAM expression in human blood.

Scope of the claims

The claims are sufficiently broad so as to encompass detecting coronary artery diseasein general, or more specifically to encompass detecting the presence of a particular type or stage of coronary artery disease, since the claims now recite that the method is for detecting or testing "a coronary artery disease." Indeed, even the claims which recite methods for detecting expression are clearly directed towards some diagnostic purpose since they set forth testing a single test subject and comparison to control populations looking for expression similarities or differences.

In addition, the "control subjects not having said coronary artery disease encompass patients with, healthy patients and patients with some other disease, such as large granular lymphocyte leukemia.

The claims do not recite the level of statistical significance that is required to be reached, and so even with the requirement of statistical significance, the claims remain quite broad since no particular level is required. The phrase "statistically significant" describes a mathematical measure of a difference between groups, not a particular level of that difference which is acceptable. There is no universal accepted level of "statistically significant."

The claims are broad in scope because they encompass that ANY level and direction of difference in gene expression between the tested subject and the healthy controls or the controls not having said coronary artery disease is indicative of said coronary artery disease, if that difference is statistically significant. That is, the claims do not set forth that one level should be higher or lower than the other, and further do not set forth how much of a "difference" between two individuals would be necessary to draw the conclusions set forth in the claims.

Teachings in the Specification/Examples

Regarding coronary artery disease, the specification provides examples 9 and 21 wherein gene expression profiles of blood samples from individuals having coronary artery disease were compared with normal individuals, that is healthy patients. Example 8 teaches that 108 different genes were differentially expressed, but CRTAM was not one of these. Example 21 teaches that 967 genes were identified as being differentially expressed, and regarding the instant claims, table 3L provides a list of these genes (Example 21). CRTAM is among the genes.

The tables list genes that were differentially expressed, but does not provide any further information regarding the level of expression. For example, the tables do not teach if the expression was higher or lower in coronary artery disease patients versus controls.

The specification does not provide any guidance as to the level of "difference" that is sufficient (1 fold, 2 fold, etc) to result in a conclusion that bladder cancer is detected, nor does the specification provide any guidance as to the direction of the difference (higher or lower expression) that is expected to be observed for any single pairing of samples. The claims rely on comparisons between a test subject and the levels of quantified RNA from different types of controls, stating that particular observations of statistically significant differences or similarity between test and control can lead to different conclusions.

The specification fails to provide information about an essential aspect of the invention, namely, the nature of the difference in expression that was observed between coronary artery disease patients and healthy patients. Furthermore, though the specification teaches that this gene is differentially expressed in coronary artery disease patients versus healthy patients, the specification teaches this is true for hundreds of genes. There is no guidance or analysis of data in the specification to suggest that this gene in particular is sufficient to conclude that coronary artery disease is present in a sample, as is instantly claimed. This information is essential to understanding and practicing the claimed invention because it is critical to knowing how to interpret a particular comparison result.

State of the Prior Art and Level of Unpredictability

The expression of genes in example 21 was tested by hybridization of samples to a microarray that contains genetic information for tens of thousands of genes. This technology

area is highly unpredictable, and as a result significant guidance is required to practice inventions using this type of data. Lee (Clinical Chemistry, 47:8, 1350-1352 (2001)) teaches that despite the technical accuracy of individual observations on an array, these data "are much more prone to numerous false-positive findings fundamentally because of (a) an extremely large number of observations and (b) a very wide dynamic range of gene expression values obtained from gene chip experiments." In view of these unpredictable aspects of applying such data, Lee teaches that replication is necessary to begin to screen out false positive results. There is no replication in the instant specification.

Furthermore, there is no analysis of all possible diseases or phenotypes to determine if the gene expression difference observed in the instant application is specific to coronary artery disease such that any difference between a test patient and blood samples from control subjects is sufficient to conclude coronary artery disease is present. For example, Loughran, JR et al. also observed that CRTAM is differentially expressed in patients having large granular lymphocyte leukemia compared to healthy patients (US 2007/0020666, p. 23). Zlontnik et al. teach that CRTAM is expressed specifically on activated class I MHC-restricted T cells, and thus differential expression in this gene might be indicative of an immune response which has activated T-cells. So first, even if one carried out the claimed analysis on a test subject, and if one observed a level of expression, it is highly unpredictable how would one begin to know if that level of expression indicated coronary artery disease, LGL leukemia, both, one but not the other, something in between or even some other condition or disorder for which the expression profile has not yet been determined. Furthermore, although CRTAM was not observed to be differentially expressed in any of the other examples in this specification, it is unknown and

unpredictable whether it would be expressed in the blood of patients having other cardiovascular diseases or any other diseases which were not tested in the instant specification or diseases which were tested in the instant specification but in a different population of test subjects, and whether this expression would be different from levels of expression in healthy controls. A method for detection which relies on a comparison between expression in the blood of a test subject and control subjects requires the knowledge of this information in order to reliably "detect" coronary artery disease, as set forth in the claims. The instant specification has not established that all difference, no matter the magnitude nor the direction, relative to any control subjects or even relative to a healthy control subject is indicative of coronary artery disease. It is not known under what circumstances the result observed in the instantly examined control and test populations would be repeatable, as the results have not been validated. But even if one were to obtain the same result, it would be unknown because applicant did not disclose the magnitude of difference in expression between coronary artery disease patients or controls, nor did applicant disclose the direction of variation. All of these inquiries are particularly important in this case since the specification is silent as to which differential expression observations would be sufficient to detect the presence of coronary artery disease.

Further, the claims of the instant application set forth the comparison of the gene expression in a single individual versus as few as two other individuals, and they set forth that a comparing gene expression between the two is "indicative of" coronary artery disease. Neither the specification nor the claims set forth a threshold of difference between an individual's expression and the control expression of CRTAM in the blood that would be sufficient to conclude that the difference in gene expression between a test individual and any type control

group is "indicative of" recited coronary artery disease. Because the claims encompass any level of altered gene expression, it is relevant to point out that the art of Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a coronary artery disease or the absence of coronary artery disease.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al. teaches that a basic statistical problem is determining when the measured differential expression

is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph). There is no replication of data in the instant specification.

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention. In particular, the specification does not provide adequate guidance to appraise one of ordinary skill in the art as to what levels of CRTAM gene expression must be observed to successfully conclude that coronary artery disease is present. Further, although the specification teaches there are differences in CRTAM levels in a coronary artery disease population versus a control patient population, the specification is silent as to the nature of the "difference" in magnitude or direction. Thus, given the lack of teaching in the specification and the highly unpredictable nature of the technology, an extensive amount of work would be required to practice the claimed invention.

In order to practice the claimed invention, one would have to undertake an extensive amount of experimentation in a highly unpredictable technology area. One would begin by trying to reproduce the results observed in the instant specification to determine if there is a relative upregulation or downregulation of CRTAM in coronary artery disease patients versus healthy control patients, as the specification does not even provide this minimal guidance. Without this knowledge one would not even begin to know how to interpret any results obtained in practicing the claimed methods. For example, consider the comparison of a test result and a control population of healthy individuals. How different from the average level of expression of healthy individuals would the test result have to be to indicate coronary artery disease? Would any difference, up or down regulation be indicative of coronary artery disease? Or could one

indicate coronary artery disease and one a different undisclosed disease? Is CRTAM expressed in the blood of individuals with a disease other than leukemia and coronary artery disease? Is this expression also diagnostic of other cancers or other diseases of the cardiovascular system or other disorders entirely unrelated to coronary artery disease? In order to reliably use a method for detecting coronary artery disease, one would first have to answer at least these questions. One would also, however, have to carry out this testing for validation, for it is possible that the result observed in the instant specification is intrinsic to the cohort of patients evaluated in applicant's study. Further, one would have to undertake experimentation to determine difference thresholds required to determine that a patient has or does not have a disease.

As discussed, this art area is highly unpredictable.

Conclusion

The claims include methods which encompass the detection in blood of the expression of CRTAM in a test subject and comparing this expression to control subjects, wherein the comparison itself "is indicative of coronary artery disease." The identification of gene differential expression/disease indication relationships is a highly unpredictable endeavor, requiring extensive experimentation. The specification provides minimal guidance. In light of the factors discussed, therefore, it is concluded that it would require undue experimentation to practice the claimed invention.

Conclusion

Response to Remarks

The rejections have been modified to address the amended claims and to address the newly added claims. Applicant states in their summary of the nature of the invention and the

scope of the claims that the claimed methods "do not permit 'any level and direction of difference in gene expression to be indicative of disease.'" The claims have been amended to require that statistically significant similarity between the test and control subjects having said coronary artery disease, and in some also cases statistically significant difference between the test subject level and controls not having said coronary artery disease or healthy controls, but still the claims are sufficiently broad so as to encompass any level or direction of difference, for the claims that recite the difference, provided the level rises to the level of "statistically significant." Further, the claims do not recite the level of statistical significance that is required to be reached, and so even with the requirement of statistical significance, the claims remain quite broad since no particular level is required.

Applicant states on page 24 of the response that the control patients do not encompass patients with some other disease such as large granular lymphocytic leukemia or bladder cancer, patients with a particular stage of coronary artery disease, etc. However, it is noted that many of these are in fact encompassed by "patients that do not have coronary artery disease."

Applicant points out, also on page 24, that claims 66-74 recite a method of testing a human for coronary artery disease but do not positively recite that the test results in an indication of coronary artery disease. However, since the claim is clearly drawn to a method for "testing for coronary artery disease" it is implied by the language of the claim that the method and the result of the methods are in fact practiced to produce a result related to "testing for coronary artery disease. Whether or not the claim specifically recites that the results are an indication that coronary artery disease is present in the test individual, reading the claims in light of their preamble and in light of the specification, it is clear that these claims are intended to lead one

practicing the method to concluding that coronary artery disease is indicated or likely to be present based on the result of the test. Otherwise, how is the recited method a test for coronary artery disease?

Likewise with regard to claims 75-83, although these claims recite that they are for detecting expression of CRTAM in human test subject, they are clearly intended for diagnostic or indication purposes, since all of the comparisons are relative to patient populations having coronary artery disease. Understanding the relationship between CRTAM expression and coronary artery disease is critical to practicing the claimed invention (i.e. the "how to use" portion of 112 1st paragraph).

Applicant argues that the fact that the claims require determination of a statistically significant similarity between the test subject and control subjects having coronary artery disease makes it unnecessary to include the direction and magnitude of the difference because no direction or magnitude information is required in order to compare for similarity, stating that the declaration exemplifies that it would not take undue experimentation to make the claimed comparisons. However, the rejection is maintained, even in light of the declaration due to the highly unpredictable nature of this technology, as discussed in the rejection. The instant specification fails to provide a critical piece of information with regard to understanding the relationship between CRTAM expression and CAD. The specification invites one of skill in the art to undertake experimentation to (a) determine the relationship between CAD and CRTAM expression and then to validate that relationship. There is a fundamental absence of information given in the specification. The declaration demonstrates that CRTAM has significantly higher

expression in CAD patients, but this does not make up for the deficiency in the specification. The claims all set forth comparing the test level to "a quantified level of RNA encoded by said gene in blood samples from control subjects..." but the specification does not provide this quantified level, or any quantified level. So, it is left to one of skill in the art to establish what is critical for the practice of the invention. While the specification may rely on the state of the prior art to help enable the invention, the specification may not rely on the state of prior art to supplement what is critical to the practice of the invention- in this case the quantified levels of control RNA encoded by the gene in the control subjects, no matter which type of control subjects. The data given in the declaration is not commensurate in scope with the data given in the specification.

Applicant states that the experimental results disclosed in the declaration merely validate the teachings of the specification, but this is not accurate. The add to the teachings in the specification since they teach that CRTAM RNA have been experimentally shown to be significantly higher in CAD patients relative to healthy controls. The claims all rely on comparison to CRTAM quantified levels that are not given in the specification.

It is not known, and unknowable from the specification if the level of expression in other diseases (such as other cardiovascular diseases) is the same as that for coronary artery disease patients. Likewise, as pointed out in the rejection this gene is differentially expressed in blood of patients with leukemia, and so it is not known if this level is the same or different as those patients with coronary artery disease. The claims recite that they are methods for "**detecting**" coronary artery disease, and so in order to detect the disease one must be able to put the result into a larger context. The claims are not limited to comparison between patients

having coronary artery disease and not having coronary artery disease, they are broadly drawn and recite control subjects having "a coronary artery disease" and control subjects not having "said coronary artery disease." There is not even a showing in the specification that the levels of this gene differ in different stages of coronary artery disease, yet applicant's claims encompass methods wherein "said coronary artery disease" is a particular stage of coronary artery disease and comparison to a level of the gene expression from a different stage of the cancer.

Applicant further argues that it does not require undue experimentation to determine the inherent direction or level of the statistically significant differential expression required, give the widely established and validated analytical tools for analyzing gene expression levels. This attorney argument is not supported by evidence on the record, for example showing an independent confirmation of the result given in the specification. The rejection discusses at length the art established need for replication in order to enable the use or a gene expression marker as a diagnostic tool, and indeed cites a post filing date reference where this is suggested for the gene that is the subject of the claimed invention. In the background of the unpredictable nature of the claimed invention, the lack of disclosure regarding the direction of the expression change and the level of the difference in coronary artery diseases and other diseases weighs heavily in the factors for determining that the claimed invention would require undue experimentation to practice.

Regarding the predictability of the invention, applicant points to the declaration which clearly indicates that CRTAM continues to demonstrate differential expression as between populations of individuals having CAD and those not having CAD. However, as previously noted, this does not provide the missing information in the declaration itself. Further, it is

unknown if the relationship observed in the experiment provided in the declaration is the same as the relationship observed using the microarray analysis. One cannot make this comparison because the data given in the specification are incomplete. Based on the disclosed fact pattern in the instant specification, one could not extrapolate that CRTAM expression is sufficient to "detect" coronary artery disease, as set forth in the claims. On cannot readily extrapolate whether or not the level of CRTAM is the same or different in coronary artery disease and other diseases such as leukemia. If the levels are the same, it would not be sufficient to show that CRTAM expression is the same as a patient with coronary artery disease in order to detect coronary artery disease. One cannot readily extrapolate that the observation made in the specification is the same universally and not cohort specific. One cannot readily extrapolate one could successfully differentiate different types or stages of coronary artery disease based on the disclosed data.

Applicant states that the results of Cheung et al. cannot be reliably extrapolated to primary blood samples since Cheung et al. are using cultured cell lines. However, this is irrelevant to the point of Cheung et al. which is that among individuals (in this case cell lines) there is natural variability in gene expression for any particular gene. Attorney arguments are not sufficient to establish that this biological fact is not the case.

Applicant disagrees with Wu that expression data needs to be interpreted in view of other biological knowledge. Wu was relied upon for much more than this simple statement. Wu discusses at length many of the factors that make gene expression analysis unpredictable. Applicant's statement that "differential gene expression which is reproducible, and is correlated with the state of health or disease of the individual does not necessarily result directly in the state

of the disease of the individual" is attorney argument which is not supported by evidence on the record. Even if the changes are a result of downstream effects of the pathogenic process, they are related to the state of disease in the individual. Applicant points out that certain prostate markers were used as biomarkers without an understanding of their function. The examiner is not trying to require an understanding of CRTAM in CAD or any other disease, nor does Wu suggest that such is necessary. The examiner is looking to the specification for adequate guidance for making and using an invention in a highly unpredictable field of endeavor.

Applicant states that the examiner appears to be asking the Applicant to enable a "gold standard" diagnostic test. The examiner is not asking such, but instead is pointing out the deficiencies in the level of teachings given in the specification in order to enable any level of diagnostic test or test directed at even suggesting that CAD is present. In this case, there is no external validation given in the specification, critical data regarding the relationship between the gene expression activity in diseased versus healthy individuals is absent, and the technology area is highly unpredictable, and the gene has been shown to be differentially expressed in the blood of patients with a different disease, to name a few problems. The examiner is not, and has not required a test with a sensitivity of 100%, contrary to applicant's suggestions.

Applicant states that in order for the test to incorrectly indicate the presence of CAD in a test individual, there must be another disease state which results in a statistically significant similarity in the level of expression as compared to expression levels in CAD. However, since, based on the specification CAD expression levels for CRTAM and other diseases are unknown, it is impossible for one of skill in the art to even begin to make this determination.

Applicant points out that Loughran looks at differential expression in PMBS or fractionated leukocytes, in contrast with the experiments performed in the instant specification. First, many of the claims at issue recite only a blood sample, and do not distinguish. Second, there is no evidence on the record to support the assertion that the differential expression observed by Loughran et al. would not be observed in total blood RNA samples. Third, the fact remains that it is unpredictable which diseases CRTAM might be differentially expressed in blood samples for, relative to controls, and Loughran et al. exemplify this. Of all possible diseases, only a small subset was tested, and only one type of cardiovascular disease. Neither the specification nor evidence on the record, however, establish CRTAM levels for even "related" diseases. The claims encompass even staging of coronary artery disease, but the specification makes no showing that CRTAM levels differ among individuals with different types or stages of coronary artery disease. Applicant undertakes a discussion of the meaning of "indication" pointing out that it is not equated with "diagnosis." The instant claims set forth that they are a method for detecting coronary artery disease. Broadly and reasonable interpreted, "detecting a coronary artery disease" means determining that it is there, and so the claims must be so enabled.

Applicant argues that even if CRTAM is differentially expressed in the blood of patients having other diseases this would not detract from the utility of the biomarkers as an indication of CAD, but would merely reduce the specificity of the biomarker. However, without further and extensive experimentation, including the analysis of other cardiovascular diseases, at the very least, one practicing the claimed invention would have no idea the specificity or sensitivity of the claimed test. Applicant undertakes a discussion of the meaning of "indication" pointing out that it is not equated with "diagnosis." The instant claims set forth that they are a method for

detecting coronary artery disease. Broadly and reasonable interpreted, "detecting a coronary artery disease" means determining that it is there, and so the claims must be so enabled.

Regarding the question of whether or not CRTAM is sufficient to conclude that coronary artery disease is present in a sample, applicant states that it is only a result of the USPTO's policy regarding restriction requirements that the Applicant has been forced to narrow the claims to a specific gene or set of genes. This argument is irrelevant to the issue of enablement. It is additionally noted there was no requirement that applicant cancel linking claims which were present in the original claim set and generic to any possible gene or combination of genes from the instant application. Second, there was no requirement that only a combination of a single gene method be elected. These were decisions made by applicant and not the office.

The rejection is maintained and updated to address the amended and newly filed claims.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete

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/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

February 4, 2008